BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

Patent Office
Canberra

I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2002950182 for a patent by PETER JAMES JENKINS as filed on 12 July 2002.

WITNESS my hand this
Second day of February 2004

J. Billingsley

JULIE BILLINGSLEY
TEAM LEADER EXAMINATION
SUPPORT AND SALES

Compounds For Medicinal Purposes

Abstract:

Application of compounds of formula (1) (Gibberellins) and their derivatives for the preparation of a pharmaceutical composition or medicaments for the treatment of diabetes and related conditions. The method results the normalization of serum glucose level and other physiological conditions.

Field of the invention:

The present invention relates to the application of a group of compounds known as Gibberellins and their derivatives for the preparation of a pharmaceutical composition for the treatment of diabetes and related conditions, as well as a method for treating these and other conditions by administering Gibberellins on a pharmaceutically acceptable salts or esters including glycoside esters, active esters or lactones. Moreover, this invention relates to the manufacturing and the use of a medicament for treating diabetes and related conditions thereof. Furthermore, the application of Gibberellins and their derivatives especially by oral, injection, transdermal patches, or by inhalation administration can be used as a substitute for insulin and/or its fragment derivatives and/or IGF (Insulin like Growth Factor) treatment or as a choice of combination therapy with insulin, its fragment derivatives, IGF, growth factors or other pharmaceutically compatible anti-diabetic agents for the treatment of diabetes and related conditions.

Background of the invention:

This invention relates to a novel application of Gibberellins in veterinary and human medicines. In particular the invention concerns Gibberellins' pharmaceutical formulations and their use for the treatment of diabetes including type 1 and type 2 diabetes and their related conditions.

Gibberellins are a series of naturally occurring compounds, which are known as plant growth regulators with wide application in the plant kingdom [1]. They have also been isolated from metabolites of some microorganisms, such as Gibberella fujikuroi [2]. Gibberellins, especially Gibberellic Acid (Gibberellin A_3), and its mixture with Gibberellin A_4 and/or A_7 which are commercially available, have been extensively applied in agriculture to increase the growth of some fruits (strawberries and grapes) and

vegetables (tomatoes, cabbages and cauliflowers), also as food additive in the malting of barley [3].

[1]. J. MacMillian, et al. "Isolation and Structure of Gibberellin From Higher Plants". Adv. Chem. Ser 28, 18~24, (1961).

[2].

(a) P.J. Curtis et al. Chem. & Ind. (London) 1066, (1954).

(b) B.E. Cross, J. Chem. Soc. 4670, (1954).

(c) P.W. Brian et al, U.S. 2,842,051.

(d) C.T. Calam et al, U.S. 2,950,288.

(e) A.J. Birch et al, U.S. 2,977,285.

[3].

(a) M. Devlin, Plant Physiology, New York, Reinhold, (1966).

(b) P.W. Brian et al, Plant Physiol, 5,669 (1955).

(c) A.K Mehta et al, J. Hostic Sci 4, 167 (1975).

(d) R.J. Weavor, Adv. Chem. Ser 28, 89 (1961).

(e) F.G. Gustafson, Plant Physical 35, 521 (1960).

(f) Fed. Reg. 25, 2162 (1960).

Gibberellin A_3 and its mixture of Gibberellin A_4 and/or A_7 can be obtained by fermentation of microorganisms such as Gibberella fujikuroi. The crude compounds can be isolated and purified by solvent extraction and recrystallization to afford a high purity crystalline product. The other derviatives of Gibberellin can be obtained by either semi-synthetic route from Gibberellin A_3 or total synthesis which have been well documented [4].

[4] .

(a) The Merck Index, 12, 4426, literatures cited herein.

(b) Furber M., et al., "New Synthesis Pathways From Gibberellins to Autheridiogens Isolated From the Fern Genus Anemia", J. of Org. Chem. vol 55, No. 15, 4860~4870 (1990).

(c) Mander L. N., et al., "C-18 hydroxylation of Gibberellins", J. C. S., Perkin Trans. 1 (17), 2893~2894 (2000).

(d) Pour M. et al., "Synthesis of 3,12-Dihydroxy-9,15-Cyclo Gibberellins", Tetrahedron 54(45), 13833~13850 (1998).

(e) Liu J. P. et al., "A General Protocol For the Hydroxylation of C-14 in Gibberellins Synthesis of 14-Beta-hydroxy-Gibberellin A_1 Methyl Ester", Tetrahedron 54(38), 11637~11650 (1998).

(f) Pour M, et al., "Synthetic and Structural Studies on Novel Gibberellins", Pure and Applied Chemistry 70(2), 351~354 (1998); "Synthesis of 12-Hydroxy-9,15-Cyclo-Gibberellins", Tetrahedron Letters, 39(14), 1991~1994 (1998); Australian J. of Chemistry 50(4), 289~299 (1997).

(g) King G. R. et al., "A New and Efficient Strategy for the Total Synthesis of Polycyclic Diterpenoids – The Preparation of Gibberellins (+/-)-GA_{103} and (+/-)-GA_{73}", J. Am. Chem. Soc. 119(16), 3828~3829 (1997).
(h) Mander L. N., "Synthsis of 12-Hydroxy-C-20-Giebberellin from Gibberellin A_3", Tetrahedron 53(6), 2137~2162 (1997) and literatures cited herein.

Furthermore, the extraction and isolation of different Gibberellins from different plants, shoots, fruits and seeds have also been widely published [5].
[5].
(a) Pearce D.W., et al., Phytochemistry, 59(6), 679~687 (2002).
(b) Chang S. T., et al., Physiologia Plantarum, 112(3), 429~432 (2001).
(c) Nakayama M. et al., Phytochemistry, 57(5), 749~758 (2001); 48(4), 587~593 (1998).
(d) Blake P. S., et al., Phytochemistry, 55(8), 887~890 (2000); 53(4), 519~528 (2000).
(e) Koshioka M., et al., J. of the Japanese Society for Horticultural Science, 68(6), 1158~1160 (1999); 67(6), 866~871 (1998).
(f) Mander L. N. et al., Phytochemistry, 49(8), 2195~2206 (1998); 49(6), 1509~1515 (1998).
(g) Wynne G. et al., Phytochemistry, 49(7), 1837~1840 (1998).

Gibberellins have previously been used for anti-inflammation, treatment of prostatitis and psoriasis, treatment of tumor, and for ulcer and wound healing [6].
[6].
(a) U.S. 4424232 1/1984 Parkinson
(b) French 2597339 10/1987
(c) U.S. 5487899 1/1996 Davis
(d) U.S. 5580857 12/1996 Oden
(e) AUS. 695054 11/1998 Wu
(f) U.S. 6121317 9/2000 Wu

We have now found application of Gibberellin or its derivatives for the treatment of diabetes including type 1 and type 2 diabetes and their related conditions.

Disclosure of the invention:

It has now been found that Gibberellins possess mammalian growth factor (such as IGF, EGF) like properties in our laboratory.

The experimental results (examples 3 and 4) suggested that Gibberellins, which are generated by plants and microbes, act as broad spectrum binders binding to a range of growth factor receptors. They differ from the growth factors found in animals, each of which has a high affinity for a specific receptor. This is the result of evolution. The

biological systems of plants and microbes produce biological substances acting on a broader (less specific) base than that of the more complex life forms such as animals.

Since Gibberellins are smaller molecules than growth factors, the binding of Gibberellins on the growth factor receptors is probably weaker. In the presence of low level of growth factors, Gibberellins bind to growth factor receptors to stimulate cell growth and other functions. Under this condition, Gibberellins perform the functions of the growth factors. In the presence of normal level of growth factors, the growth factors bind to their receptors more readily due to their higher affinity for those receptor sites. The physical bulkiness of these growth factors leave no room or very little room at the receptor sites for which Gibberellins can bind. This results in Gibberellins being ineffective when growth factors are present in sufficient quantities. This mechanism provides a very good profile for Gibberellins acting as a substitute for growth factors including IGF since the presence of excess Gibberellins will not interfere with the normal functions of these growth factors.

It is known that insulin, IGF and EGF receptors are all in the same family and their structures are expected to be have 90% similarity (Ward C.M. et al., Nature, 394 (6691), 395~399 (1998); Molecular pathology, 54(3), 125~132 (2001)). Therefore, it may be logically expected that Gibberellins could play a role not only as a substitute for growth factors but also as a substitute for insulin.

Diabetes mellitus is a chronic disorder manifested by hyperglycemia and altered lipid and protein metabolism. According to the American Diabetes Association, more than 13 million people in the U.S. suffer from diabetes, and each year some 650,000 new cases are identified. The introduction of insulin and of sulfonyl ureas represented important landmarks in the treatment of diabetes mellitus. Insulin like growth factor – 1 (IGF-1), a molecule with structure homology to insulin, has its own specific receptor, the type-1 IGF receptor, through which it elicits a variety of metabolic effects that are similar to insulin. The discovery of the active region of human growth factor responsible for the insulin like actions of the molecule has led to the development of its fragment as new anti-diabetic peptide agent. It is also known that growth factors are polypeptides that regulate the replication, differentiation and metabolic homeostasis cells. They increase the growth and/or survival of neurons. IGF-2 is known to increase the rate of nerve regeneration, in pre-clinical testing for the treatment of various neurological disorders including diabetic neuropathies. Furthermore, elevated intracellular concentrations of c-AMP potentiate glucose-dependent insulin secretion from pancreatic β-cells. It is known that Gibberellins increase the activity of adenylate and gryanylate cyclase. The intracellular concentrations of c-AMP and c-GMP may therefore be increased by the administration of Gibberellins as the consequence to potentiate glucose-dependent insulin secretions from pancreatic β-cells. From the review described above, it may be logically expected to apply Gibberellins for the treatment of diabetes.

The animal experiment results (examples 5 & 6) showed diabetic rats treated with 5mg/kg of Gibberellin A_3 or a mixture of A_3 and A_4 or A_7 returned their serum glucose level to the normal, as well as their body weights. It indicated that Gibberellins may be effective in the treatment of diabetes.

In combination with the fact that the toxicity to mammals of Gibberellin A_3 is extremely low. The acute oral LD_{50} for rats and mice is reported to be 6.3g/kg [7a] and >15g/kg [7b] respectively. In 90-day feeding trials, the no effect level for rats and dogs was >1g/kg/day [7b]. It is non-irritating to skin and eyes [7b]. No indication has been found of carcinogenicity [7c]. Classifications: WHO Toxicity Class Table 5 (least hazardous class product, unlikely to present acute hazard in normal use); EPA Toxcity class III (second least hazadous classification).

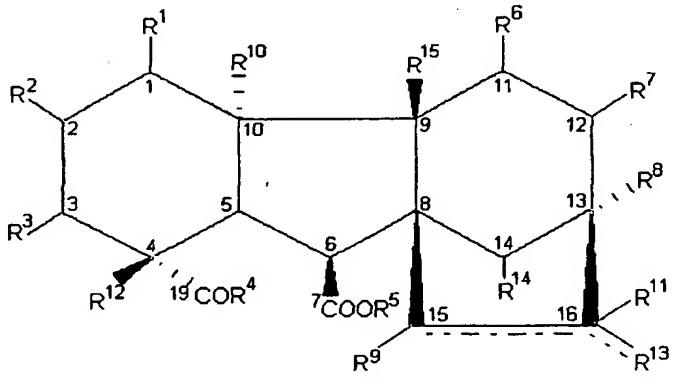
[7].

(a) NTP Chemical Repository,
http://ntpserver.niehs.nih.gov/htdocs/CHEM_H&S/NTP_CHEM7/Radian77-06-5.html

(b) The Agrochemicals Handbook, Royal Society of Chemistry, August 1991.

(c) Gold L. S., Slone T. H., Ames B. N. (2001), Pesticide Residues in Food and Cancer Risk: A Critical Analysis, Publications from the Carcinogenic Potency Project, in Handbook of Pesticide Toxicity, Second Edition, (R. Krieger, ed.), Academic Press.

Thus this invention provides an aspect use of compounds of formula (1) (Gibberellins) and their derivatives for the treatment of diabetes and related conditions. Furthermore, this invention would be extended as described in the "Field of the invention".



Formula (1)

wherein

R^1 is H or a group $-O-R^{20}$, where R^{20} is H, or together with R^2 or R^{10} forms a bond (C_1–C_2 or C_1-C_{10} double bond, respectively);

R^2 is H or a group –O-R^{21}, where R^{21} is H, a glycosylic ether group (glycoside ether) or together with R^4 forms a bond (lactone) or together with R^1 or R^3 forms a bond (C_1-C_2 or C_2-C_3 double bond, respectively);

R^3 is H, =O, or –O-R^{22}, where R^{22} is H or a glycosylic ether group (glycoside ether), or together with R^2 forms a bond (C_2-C_3 double bond);

R^4 is OH, or –OR^{23}, where R^{23} is unsubstituted or substituted $C_{1\sim20}$ alkyl, allyl, aryl, arylalkyl, amidine, -$NR^{24}R^{25}$ or an unsaturated or saturated ring containing one or more hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur; R^{24} and R^{25} may or may not be the same, are hydrogen, or $C_{1\sim20}$ alkyl, allyl, aryl, arylalkyl or an unsaturated or saturated ring containing one or more hetero-atoms slected from the group consisting of nitrogen, oxygen and sulphur; R^4 together with R^{21} or R^{28} forms a bond (lactone);

R^5 is H or a glycosylic ester (glycoside ester) group, or unsubstituted or substituted (e.g. haloginated) $C_{1\sim20}$ alkyl esters, allyl esters, aryl esters, arylalkyl esters, active esters (such as phenacyl ester, pivaloyl ester);

R^6 is H or OH or together with R^7 forms a bond (C_{11}-C_{12} double bond);

R^7 is H, =O, or –OR^{26}, where R^{26} is H or a glycosylic ether group (glycoside ether) or together with R^6 forms a bond (C_{11}-C_{12} double bond);

R^8 is H, hydroxyl, mercaptan, or halogen (e.g. F, Cl), amino, azido, $NR^{24}R^{25}$, unsubstituted or substituted (e.g. halogenated) $C_{1\sim20}$ alkyl, allyl, aryl, or arylalkyl, or –OR^{27}, where R^{27} is a glycosylic ether group (glycoside ether);

R^9 is H or OH, or together with R^{15} forms a bond (C_9-C_{15} bond);

R^{10} is H, CH_3, CHO, COOH, or a glycosylic ester (glycoside ester) of said COOH, CH_2O-R^{28} or –OR^{28}, where R^{28} is H or together with R^4 forms a bond (lactone) or together with R^1 forms a bond (C_1-C_{10} double bond);

R^{11} is OH or absent;

R^{12} is CH_3, CH_2OH, COOH or a glycosylic ester (glycoside ester) of said COOH;

R^{13} is methylene, or a divalent hetero-atom, or NR^{29}, where R^{29} is NR^{30} or OR^{30} where R^{30} is H, or $C_{1\sim20}$ alkyl, aryl, alkylaryl; when R^{11} is absent, a double bond is present between C_{16} and R^{13};

R^{14} is H or OH;

R^{15} is H, or together with R^9 forms a bond (C_9-C_{15} bond);

And pharmaceutically acceptable derivatives, lactones, esters and salts including alkali metal salts (e.g. Na^+, K^+), alkaline earth metal salts (e.g. Ca^{2+}, Mg^{2+}), metal salts (e.g. Zn^{2+}, Al^{3+}), and salts of ammonium, organic bases (such as $NR^{16}R^{17}R^{18}R^{19}$ where R^{16}, R^{17}, R^{18}, R^{19}, which may be the same or not the same, are hydrogen, $C_{1\sim20}$ alkyl, alkanol, arryl) thereof.

The dotted line together with the solid line indicate that a double bond may be situated between two of the three carbon atoms connected by the dotted and solid lines; with the proviso that a double bond is not present if R^{11} is an OH group.

Since Formula (1) complies with normal valence rules, this leads to the further provisos as follows:
R^1 and R^2 cannot form a bond if R^{10} and R^1 and/or R^2 and R^3 form a bond; R^{10} and R^1 cannot form a bond if R^{10} and R^{23} form a bond; R^2 and R^1 or R^2 and R^3 cannot form a bond if R^4 and R^{21} form a bond.

In the case of Gibberellin A_3, R^1 together with R^2 forms a bond (C_1-C_2 double bond); R^3 is β-OH, R^4 together with R^{28} forms a bond (lactone); R^5, R^6, R^7, and R^9 are hydrogens, R^8 is OH, R^{11} is absent; R^{12} is methyl; R^{13} is methylene, a double bond is present between C_{16} and R^{13}; R^{14} and R^{15} are hydrogens.

MD-960 – TRIAL 3

METHODS

Male Wistar rats (290-330g) were weighed and lightly anaesthetised (4% halothane, 2:1 O_2/N_20) so that blood glucose levels could be measured via a tail vein sample, using a Precision Q.I.D. glucometer. Diabetes was then induced by a single tail vein injection of streptozotocin (STZ, 60 mg/kg), which was dissolved immediately prior to use in citrate buffer (50mM citric acid and 50mM trisodium citrate; pH 4.5). An equivalent volume of citrate buffer was injected into age-matched control rats.

Rats were housed in groups of two for the next two weeks. Animal house temperature was maintained at 20°C (±2°C) with a 12 hour light/dark cycle, and rats were allowed free access to food and water.

Ethical approval for all experiments was obtained from the Pharmacology Animal Ethics Committee.

DRUG ADMINISTRATION AND DAILY MONITORING PROTOCOL

Forty eight hours after the administration of STZ (60mg/kg), a blood glucose sample was taken and animals with blood glucose levels ≥16mM were considered to be diabetic. Rats were then randomly divided into one of the following three groups:

(1) insulin-treated (4U; *s.c.*) diabetic rats receiving insulin daily for the entire trial,

(2) sub-maximal insulin- treated (2U; *s.c.*) diabetic rats receiving a daily dose of insulin for the entire trial. These animals also received an oral dose of MD-960 (5mg/kg) three times daily from days 42-46, and

(3) sub-maximal insulin- (2U; *s.c.*) and MD-960-treated (5mg/kg) diabetic rats receiving a daily dose of insulin and MD-960. MD-960 was initially given *s.c.*, but was administered *i.p.* from days 26-46. This group was given an additional dose of MD-960 (5mg/kg; i.p.) (ie. once in the morning and again in the afternoon) from days 38-46.

The slow-acting, Lente Monotard insulin was used and MD-960 was made up as required in distilled water immediately prior to use.

Blood glucose readings were obtained two hours after the administration of drug(s), every three days. From days 36-46 blood glucose readings were obtained five hours after the administration of insulin and/or MD-960.

Rats were sacrificed by a blow to the head and decapitation on day 46 of the trial in accordance with the ethics obtained for this study.

MD-960 TRIAL 3

RAW DATA - BODY WEIGHT

CODE	TREATMENT	6/5/02	8/5/02	9/5/02	10/5/02	11/5/02	12/5/02	13/05/02	14/05/02	15/05/02	16/05/02	17/05/02	18/05/02	19/05/02	20/05/02	21/05/02	22/05/02	23/05/02	24/05/02	25/05/02	26/05/02	27/05/02
PINK 1	INSULIN (4U)	356	331	332	330	326	325	342	336	332	344	338	336	350	318	343	343	341	343	346	341	319
PINK 2	INSULIN (4U)	370	334	345	338	332	325	328	337	336	341	337	330	335	300	323	326	327	334	339	341	339
PINK 3	INSULIN (4U)	360	325	328	332	330	320	317	332	322	334	325	323	333	330	331	331	336	337	354	367	352
PINK 4	INSULIN (4U)	350	324	322	316	323	314	319	329	322	329	319	322	352	333	328	329	331	340	345	341	340
BLUE 1	INSULIN (2U)	360	331	334	332	327	326	330	325	331	337	330	330	342	338	334	335	333	337	340	337	340
BLUE 2	INSULIN (2U)	345	318	316	317	317	308	317	322	317	322	308	312	317	309	313	317	321	322	321	320	320
BLUE 3	INSULIN (2U)	347	319	327	327	325	320	325	330	328	338	331	334	347	343	340	345	334	345	348	348	343
BLUE 4	INSULIN (2U)	366	340	344	343	336	332	340	344	340	347	348	340	347	344	340	336	337	333	337	336	337
GREEN 1	MD-960 + INSULIN	319	298	301	299	310	298	308	309	315	317	322	312	323	318	324	327	331	333	336	337	337
GREEN 2	MD-960 + INSULIN	317	302	306	302	308	311	316	319	315	321	316	319	331	330	329	333	334	339	340	344	334
GREEN 3	MD-960 + INSULIN	355	332	336	337	334	338	342	340	348	356	344	349	362	354	349	353	362	360	371	363	373
GREEN 4	MD-960 + INSULIN	325	304	308	312	304	302	303	310	312	322	317	323	335	325	323	325	326	335	333	338	340

BODY WEIGHT - % INCREASE/DECREASE

CODE	TREATMENT	6/5/02	8/5/02	9/5/02	10/5/02	11/5/02	12/5/02	13/05/02	14/05/02	15/05/02	16/05/02	17/05/02	18/05/02	19/05/02	20/05/02	21/05/02	22/05/02	23/05/02	24/05/02	25/05/02	26/05/02	27/05/02
PINK 1	INSULIN (4U)	100	92.97753	93.25843	92.69663	91.57303	91.29213	96.06742	94.38202	93.25843	96.62921	94.94382	94.38202	98.31461	89.32584	96.34831	96.34831	95.78652	96.34831	97.75281	95.78652	89.60674
PINK 2	INSULIN (4U)	100	100	103.2934	101.1976	99.4012	97.30539	98.20359	100.8982	100.5988	102.0958	100.8982	98.8024	100.2994	89.82036	96.70659	97.60479	97.90419	100	101.497	102.0958	101.497
PINK 3	INSULIN (4U)	100	100	100.9231	102.1538	101.5385	98.46154	97.53846	102.1538	99.07692	102.7692	100	99.38462	102.4615	101.5385	101.8462	101.8462	104	103.6923	108.9231	112.9231	108.3077
PINK 4	INSULIN (4U)	100	100	99.38272	97.53086	99.69136	96.91358	98.45679	101.5432	99.38272	101.5432	98.45679	99.38272	108.642	102.7778	101.2346	101.5432	102.1605	104.9383	106.4815	105.2469	104.9383
BLUE 1	INSULIN (2U)	100	91.94444	92.77778	92.22222	90.83333	90.55556	91.66667	90.27778	91.94444	93.61111	91.66667	91.66667	95	93.33333	92.77778	93.05556	92.5	93.61111	94.44444	93.61111	94.44444
BLUE 2	INSULIN (2U)	100	92.17391	91.5942	91.88406	91.88406	89.27536	91.88406	93.33333	91.88406	93.33333	89.27536	90.43478	91.88406	89.56522	90.72464	91.88406	93.04348	93.33333	93.04348	92.75362	92.75362
BLUE 3	INSULIN (2U)	100	91.93084	94.23631	94.23631	93.65994	92.21902	93.65994	95.10086	94.5245	97.40634	95.38905	96.2536	100	98.84726	97.98271	99.42363	96.2536	99.42363	100.2882	100.2882	98.84726
BLUE 4	INSULIN (2U)	100	92.69617	93.88907	93.71585	91.80328	90.71038	92.89617	93.98907	92.89617	94.80874	95.35519	92.89617	94.80874	93.98907	92.89617	92.34973	92.0765	90.98361	92.0765	91.80328	92.0765
GREEN 1	MD-960 + INSULIN	100	93.41693	94.35737	93.73041	97.17868	93.41693	96.55172	96.8652	98.74608	99.37304	100.9404	97.80564	101.2539	99.68652	101.5674	102.5078	103.7618	104.3887	105.3292	105.6426	105.6426
GREEN 2	MD-960 + INSULIN	100	95.26814	96.52997	95.26814	97.16088	98.10726	99.68454	100.6309	99.36909	101.2618	100.3155	100.6309	104.4164	104.1009	103.7855	105.0473	105.3628	106.9401	107.2555	108.5174	105.3628
GREEN 3	MD-960 + INSULIN	100	93.52113	94.64789	94.92958	94.08451	95.21127	96.33803	95.77465	98.02817	100.2817	96.90141	98.30986	101.9718	99.71831	98.30986	99.43662	101.9718	101.4085	104.507	102.2535	105.0704
GREEN 4	MD-960 + INSULIN	100	93.53846	94.76923	96	93.53846	92.92308	93.23077	95.38462	96	99.07692	97.53846	99.38462	103.0769	100	99.38462	100	100.9231	103.0769	102.4615	104	104.6154

RAW DATA - BLOOD GLUCOSE

CODE	TREATMENT	6/5/02	8/5/02	9/5/02	10/5/02	11/5/02	12/5/02	13/05/02	14/05/02	15/05/02	16/05/02	17/05/02	18/05/02	19/05/02	20/05/02	21/05/02	22/05/02	23/05/02	24/05/02	25/05/02	26/05/02	27/05/02
PINK 1	INSULIN (4U)	6			5.9			6.3			2.6			5.9			3.6			4.5		
PINK 2	INSULIN (4U)	6.5			7.3			6.1			3.4			15.3			5.8			13.5		
PINK 3	INSULIN (4U)	6.7			5.5			5.2			4.8			13.1			8.3			11.5		
PINK 4	INSULIN (4U)	6.6			6.7			3.9			4.5			8.9			5.6			14.2		
BLUE 1	INSULIN (2U)	7.2			11.3			5.5			5.5			24			14.5			19.8		
BLUE 2	INSULIN (2U)	6.2			7			21.5			12.5			20.5			6.6			12.3		
BLUE 3	INSULIN (2U)	7.2			6			19.9			18.2			14.6			6.2			13.1		
BLUE 4	INSULIN (2U)	6.4			11.2			24.6			15.3			21.6			16			17.1		
GREEN 1	MD-960 + INSULIN	7.6			5.9			20.3			9.5			9.3			7.4			13.3		
GREEN 2	MD-960 + INSULIN	6			5.2			17.7			4.3			10.5			4.7			8.1		
GREEN 3	MD-960 + INSULIN	6			9.6			18.7			6			19			5.8			3.4		
GREEN 4	MD-960 + INSULIN	6.4			12.4			8.2			6.5			23.2			5.8			6		

GROUP DATA - BODY WEIGHT

CODE	TREATMENT	6/5/02		8/5/02		9/5/02		10/5/02		11/5/02		12/5/02		13/05/02		14/05/02		15/05/02		16/05/02		17/0
PINK	INSULIN (4U)	359	4.203173	328.5	2.397916	331.75	4.871259	329	4.554747	327.75	2.015564	321	2.614065	326.5	5.693564	333.5	1.848423	328	3.559026	337	3.391185	329.75
BLUE	INSULIN (2U)	354.5	5.074446	327	5.244044	330.25	5.693148	329.75	5.406401	326.25	3.902456	321.5	5.123475	326	4.813176	330.25	4.871259	329	4.743416	338	5.18009	329.5
GREEN	MD-960 + INSULIN	329	8.831761	309	7.767453	312.75	7.888547	312.5	8.62651	314	8.78233	312.25	9.003472	317.25	8.673475	319.5	7.193747	322.5	8.529381	329	9.064583	325.25

GROUP DATA - BLOOD GLUCOSE

CODE	TREATMENT	6/5/02		10/5/02		13/05/02		16/05/02		19/05/02		22/05/02		25/5/02	
PINK	INSULIN (4U)	6.45	0.155456	6.35	0.403113	5.375	0.546771	3.825	0.507239	10.8	2.104757	5.825	0.96296	10.925	2.216745
BLUE	INSULIN (2U)	6.75	0.262996	9.375	1.101798	17.875	4.238784	12.875	2.719796	20.225	2.009301	10.825	2.574353	15.575	1.756595
GREEN	MD-960 + INSULIN	7	0.262996	8.275	1.101798	16.225	4.238784	8.575	2.719796	15.5	2.009301	5.925	2.574353	7.7	1.756595

GROUP DATA - % BODY WEIGHT

CODE	TREATMENT	6/5/02		8/5/02		9/5/02		10/5/02		11/5/02		12/5/02		13/05/02		14/05/02		15/05/02		16/05/02		17/0
PINK	INSULIN (4U)	100	0	98.24438	1.755618	99.21441	2.142037	98.39474	2.144794	98.05101	2.210585	95.99316	1.601084	97.56857	0.535922	99.74432	1.80572	98.07922	1.840194	100.7594	1.399351	98.5747
BLUE	INSULIN (2U)	100	0	92.23634	0.226902	93.14934	0.608493	93.01461	0.569379	92.04515	0.58882	90.69008	0.802605	92.52671	0.463087	93.17526	1.032418	92.81229	0.615999	94.78988	0.929034	92.92157
GREEN	MD-960 + INSULIN	100	0	93.93816	0.444802	95.07811	0.492261	94.98203	0.473236	95.49063	0.975851	94.91483	1.172257	96.45127	1.316098	97.16385	1.197403	98.03583	0.731818	99.99837	0.49301	98.92394

28/05/02	29/05/02	30/05/02	31/05/02	1/6/02	2/6/02	3/6/02	4/6/02	5/6/02	6/6/02	7/6/02	8/6/02	9/6/02	10/6/02	11/6/02	12/6/02	13/06/02	14/06/02	15/06/02	16/06/02	17/06/02	18/06/02	19/06/02	20/06/02	21/06/02
355	360	363	375	374	368	374	365	364	364	367	370	377	374	378	380	377	378	380	374	379	380	387	388	380
343	345	347	337	348	340	355	338	347	345	353	341	347	348	348	347	352	357	358	351	356	358	355	364	359
349	350	355	354	360	359	366	364	360	350	353	364	359	362	364	368	362	357	366	361	367	359	362	367	372
341	345	351	354	349	351	357	347	355	351	355	358	353	361	356	360	356	358	349	351	357	361	363	355	362
336	347	341	347	347	355	354	351	352	361	353	344	354	352	354	344	343	350	353	350	348	355	358	350	352
321	330	323	332	321	330	338	330	334	332	335	338	339	342	338	342	339	335	338	340	338	333	336	330	339
352	347	358	363	356	362	363	345	355	360	347	352	369	365	360	361	353	359	362	360	362	355	357	348	356
341	345	339	340	336	346	347	346	332	335	323	322	319	327	337	334	323	321	321	321	322	318	304	311	319
334	331	335	340	343	343	344	349	347	351	351	349	348	349	354	353	349	355	354	352	353	360	356	360	356
349	345	343	350	350	359	361	361	364	364	364	365	367	369	371	368	374	378	379	374	373	380	377	383	379
365	362	367	364	373	379	370	381	376	374	379	381	387	383	387	390	385	391	380	388	391	387	385	391	388
340	343	343	336	342	348	349	356	348	348	346	349	349	351	357	357	356	360	355	360	364	357	381	362	359

28/05/02	29/05/02	30/05/02	31/05/02	1/6/02	2/6/02	3/6/02	4/6/02	5/6/02	6/6/02	7/6/02	8/6/02	9/6/02	10/6/02	11/6/02	12/6/02	13/06/02	14/06/02	15/06/02	16/06/02	17/06/02	18/06/02	19/06/02	20/06/02	21/06/02
99.7191	101.1236	101.9663	105.3371	105.0562	103.3708	105.0562	102.5281	102.2472	102.2472	103.0899	103.9326	105.6989	105.0562	106.1798	106.7416	105.6989	106.1798	106.7416	105.0562	106.4607	106.7416	108.7079	108.427	106.7416
102.6946	103.2934	103.8922	100.8982	104.1916	101.7964	108.2874	100.5988	103.8922	103.2934	105.6886	102.0958	103.8922	103.5928	103.5928	103.8922	105.3892	106.8882	107.1856	105.0898	106.5886	107.1856	106.2874	108.982	107.485
107.3848	107.6823	109.2308	108.9231	110.7692	110.4615	112.6154	112	110.7692	107.6823	108.6154	112	110.4615	111.3846	112	113.2308	111.3846	109.8462	112.6154	111.0769	112.9231	110.4615	111.3846	112.9231	114.4615
105.2469	106.4815	108.3333	109.2593	107.716	108.3333	110.1852	107.0988	109.5679	108.3333	109.5679	110.4938	108.9506	111.4198	109.8765	111.1111	109.8765	110.4938	107.716	108.3333	110.1852	111.4198	112.037	109.5679	111.7284
93.33333	96.36889	94.72222	96.36889	96.36889	98.61111	98.33333	97.5	97.77778	100.2778	98.05556	95.55556	98.33333	97.77778	98.33333	95.55556	95.27778	97.22222	98.05556	97.22222	96.66667	98.61111	99.44444	97.22222	97.77778
93.04348	95.65217	93.62319	96.23188	93.04348	95.65217	97.97101	95.65217	96.81159	96.23188	97.10145	97.97101	98.26087	99.13043	97.3913	99.13043	98.26087	97.10145	97.97101	98.55072	97.97101	96.52174	97.3913	95.65217	98.26087
101.4409	100	103.17	104.611	102.5937	104.3228	104.611	99.42363	102.3055	103.7464	100	101.4409	106.3401	105.1873	103.7464	104.0348	101.7291	103.4582	104.3228	103.7464	104.3228	102.3055	102.8818	99.71182	102.5937
93.1894	94.2623	92.82295	92.89617	91.80328	94.53552	94.80874	94.53552	90.71038	91.53005	88.25137	87.97814	87.15847	89.34426	92.0765	91.25683	88.25137	87.70492	87.70492	87.70492	87.97814	88.3388	83.06011	84.97268	87.15847
104.7022	103.7818	105.0157	106.5831	107.5235	107.5235	107.837	109.4044	108.7774	110.0313	110.0313	109.4044	109.0909	109.4044	110.9718	110.6583	109.4044	111.2853	110.9718	110.3448	110.6583	112.8527	111.5987	112.8527	112.2257
110.0946	108.8328	108.2019	110.4101	110.4101	113.2492	113.8801	113.8801	114.8265	114.8265	114.8265	115.142	115.7729	116.4038	117.0347	116.0883	117.9811	118.612	119.5584	117.9811	117.6656	119.8738	118.9274	120.8202	119.5584
102.8169	101.9718	103.3803	102.5352	105.0704	106.7606	104.2254	107.3239	106.4789	105.3521	106.7606	107.3239	109.0141	107.6873	109.0141	109.8592	108.4507	110.1408	107.0423	109.2958	110.1408	109.0141	108.4507	110.1408	109.2958
104.6154	105.5385	105.5385	103.3846	105.2308	107.0769	107.3846	109.5385	107.0769	107.0769	106.4615	107.3846	107.3846	108	109.8462	109.8462	109.5385	110.7692	109.2308	110.7692	112	109.8462	111.0769	111.3846	110.4615

28/05/02	29/05/02	30/05/02	31/05/02	1/6/02	2/6/02	3/6/02	4/6/02	5/6/02	6/6/02	7/6/02	8/6/02	9/6/02	10/6/02	11/6/02	12/6/02	13/06/02	14/06/02	15/06/02	16/06/02	17/06/02	18/06/02	19/06/02	20/06/02	21/06/02	21/06/02
4.1			3			3.4			3.5			3.2			1.9		3.1			4.4		3.9		3.7	2.1
9.2			4.7			22.01			7.3			6.3			4.1		5			5.6		4.9		6.9	3.4
4.9			3.9			5.8			4.9			5.9			3.1		4			4.8		9.7		5	4.6
8.9			5.8			6.4			4.6			2.9			3.8		2.7			6.4		9.3		3.9	2.2
18.2			11.6			26.2			17.6			18.2			10		9.7			12.9		13.5		11.3	5.1
15.9			13.1			18.3			15.7			17.3			17.9		14.5			18.2		15.8		16.6	13.9
10.4			11.4			6.8			9.8			10			8.7		7.2			20.9		6.8		9.3	3
14.1			17.2			18.2			16.6			16.1			13.1		9.3			26.5		19		13.6	4.8
18			7.3			7.1			5.3			6			4.8		10.8			8.1		3.9		4.9	3.8
9.5			6.9			6.3			3.5			3.8			3.2		3.5			4.8		7		3.6	6.4
4.4			4.9			6.4			4.5			3.3			6.3		11.4			5.8		3.2		3.8	4.7
4.5			5			10.7			4			3.6			6.4		10.8			11.2		3.6		3.3	8.5

5/02		18/05/02		19/05/02		20/05/02		21/05/02		22/05/02		23/05/02		24/05/02		25/5/02		26/05/02		27/05/02		28/05/02		29/05/02		30/0
4.643544	327.75	3.275541	342.5	4.941322	320.25	7.48749	331.25	4.25	332.25	3.727712	334.25	3.198307	338.5	1.936492	346.5	3.122499	347.5	6.5	337.5	6.837397	347	3.162278	350	3.535534	354	
8.391464	329	8.027714	338.25	7.180703	333	8.195527	331.75	6.408003	333.75	5.98343	331.25	3.520772	334.25	4.784959	336.5	5.664215	335.25	5.764475	335	5.147815	337.5	6.435578	342.25	4.110454	340.25	
6.342647	330.3333	9.404491	337.75	8.459462	331.75	7.81425	331.25	6.060459	334.5	6.396614	338.75	7.848177	341.75	6.209871	345	8.784456	345.5	8.034622	346	9.082951	347	6.745389	345.25	6.381941	347	

28/05/02		31/05/02		3/6/02		6/6/02		9/6/02		12/6/02		14/6/2002		17/6/2002		19/06/02	
6.775	1.325	4.35	0.595119	9.4025	4.252177	5.075	0.800391	4.575	0.886355	3.225	0.488834	3.7	0.511534	5.3	0.443471	6.95	1.488568
14.85	1.648481	13.325	1.346214	16.825	4.02707	14.925	1.751844	15.4	1.850676	12.425	2.045065	10.175	1.542387	19.825	2.830599	13.775	2.584046
9.1	1.648481	6.025	1.346214	7.625	4.02707	4.325	1.751844	4.175	1.850676	6.175	2.045065	9.125	1.542387	7.475	2.830599	4.425	2.584046

5/02		18/05/02		19/05/02		20/05/02		21/05/02		22/05/02		23/05/02		24/05/02		25/5/02		26/05/02		27/05/02		28/05/02		29/05/02		30/0
1.311085	97.98794	1.209755	102.4294	2.237289	95.86561	3.643178	99.03391	1.454317	99.33562	1.387323	99.9628	1.66874	101.2447	1.939869	103.6636	2.503899	104.0131	3.5621	101.0874	4.0716	103.7613	1.653599	104.6477	1.496824	105.8557	
1.496879	92.81281	1.252153	95.4232	1.683975	93.93372	1.905917	93.59532	1.545078	94.17824	1.764966	93.4684	0.949258	94.33792	1.794745	94.96315	1.840356	94.61405	1.927073	94.53046	1.522641	95.24678	2.065565	96.57584	1.22357	98.0346	
1.000532	99.03276	0.626252	102.8798	0.689677	100.8764	1.07714	100.7618	1.214507	101.7479	1.286495	103.0049	0.980375	103.9535	1.167427	104.8883	0.993001	105.1034	1.331826	105.1728	0.219474	105.5573	1.573627	105.0282	1.462893	105.5341	

502	31/05/02		1/6/02		2/6/02		3/6/02		4/6/02		5/6/02		6/6/02		7/6/02		8/6/02		9/6/02		10/6/02		11/6/02		12/
3.41565	355	7.778175	357.75	6.060459	354.5	5.95119	363	4.377975	353	7.011895	356.5	3.662677	352.5	4.051749	357	3.366502	358.25	6.25	359	6.480741	360.75	5.735489	361	6.757712	363.75
7.157455	345.5	6.589132	340	7.538789	348.25	6.90883	350.5	5.299371	343	4.527693	343.25	5.96343	347	7.820912	339.5	6.652067	339	6.350853	345.25	10.68	346.5	8.025999	346.75	8.046693	345.25
6.928203	347.5	6.238322	352	7.22265	362	9.073772	356	5.87367	361.75	6.872348	359.25	7.384048	359.25	8.019067	360	7.382412	361	7.659417	362.75	9.18872	363	8.041559	367.25	7.553972	367

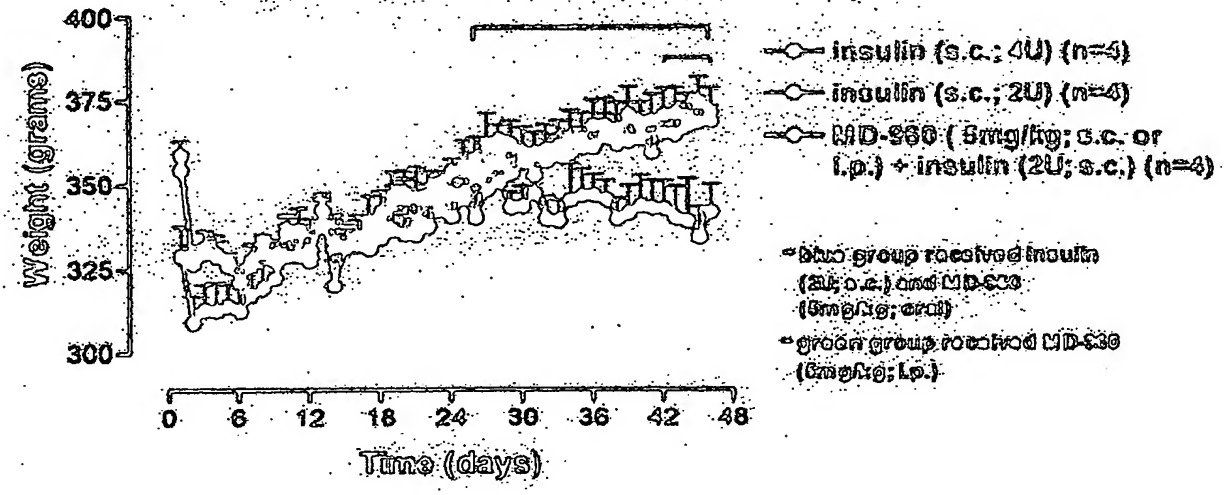
21/06/02 (2hr)		21/06/02 (6hr)	
4.875	0.733002	3.076	0.587899
12.75	1.579293	6.7	2.444381
3.9	1.579293	5.85	2.444381

502	31/05/02		1/6/02		2/6/02		3/6/02		4/6/02		5/6/02		6/6/02		7/6/02		8/6/02		9/6/02		10/6/02		11/6/02		12/
1.744337	106.1044	1.949174	106.9333	1.482326	105.9905	2.03986	108.536	1.744669	105.5584	2.543739	106.6191	2.091022	105.3916	1.533969	106.7404	1.47034	107.1306	2.425537	107.3008	1.480315	107.8633	2.064885	107.9123	1.875681	108.7439
2.416798	97.913	3.484662	95.81347	3.408946	98.17015	3.093149	99.13024	2.888406	96.53711	1.478822	96.60915	3.348745	97.16945	3.557575	95.11761	3.533618	95.79669	4.035566	97.25313	5.560125	97.88734	4.615538	97.73807	3.373287	98.14062
1.001034	105.4433	2.49547	106.9038	1.753777	109.0289	2.112131	108.4967	2.842019	110.2475	1.925525	109.4608	2.688416	109.0852	2.913521	109.3495	2.739843	109.9502	2.595951	110.7239	2.567956	110.7637	2.820229	111.965	2.548215	111.9312

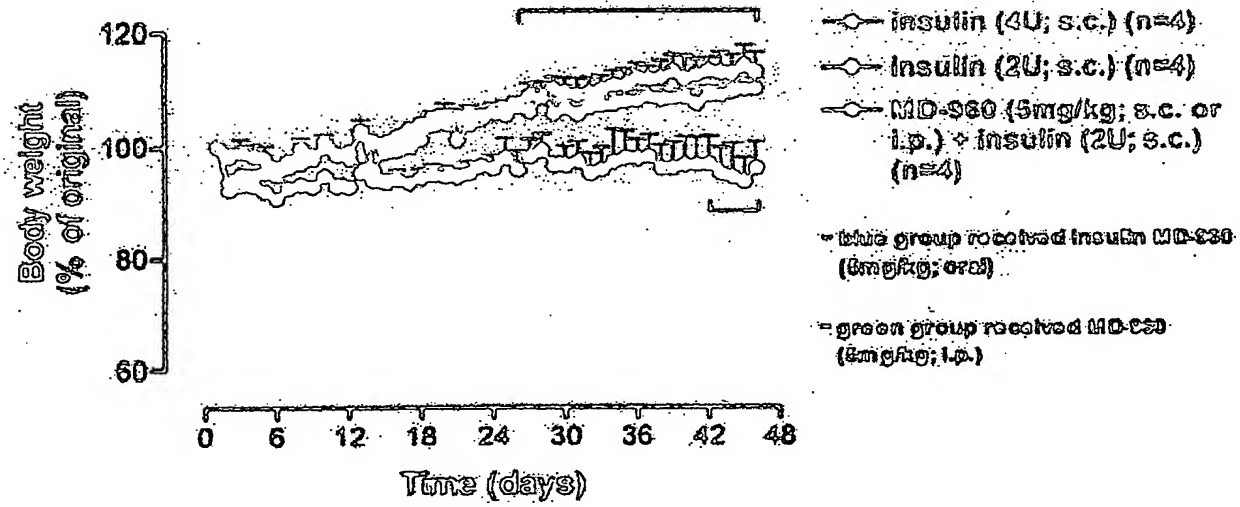
I/02	13/06/02		14/06/02		15/06/02		16/06/02		17/06/02		18/06/02		19/06/02		20/06/02/		21/06/02	
6.932717	361.75	5.482928	362.5	5.17204	363.25	6.574889	359.25	5.452448	364.75	5.35996	364.5	5.204165	366.75	6.980628	368	6.519202	366.25	4.802343
5.877074	339.5	6.238322	341.25	6.370335	343.5	8.9881	342.75	8.320407	342.5	8.421203	339.75	9.463747	338.75	12.64499	334.25	8.872946	341.5	8.331668
8.296588	368	8.238099	370.5	8.170067	367	7.22265	368.5	7.932003	370.25	8.035079	371	7.382412	369.75	6.774648	374	7.891987	371	7.449832

I/02	13/06/02		14/06/02		15/06/02		16/06/02		17/06/02		18/06/02		19/06/02		20/06/02/		21/06/02	
2.107207	108.1373	1.475706	108.3515	1.08798	108.5647	1.364853	107.3891	1.449736	109.0389	1.55619	108.9521	1.168136	109.6042	1.319501	109.975	1.00992	110.1041	1.820982
3.721673	96.08045	4.040547	96.08819	4.575718	96.66623	4.841317	96.66735	4.725555	96.75731	4.757153	95.05534	4.667135	94.44442	5.908705	93.44556	4.395544	96.00433	4.596384
2.078561	111.9901	3.01191	113.174	2.725028	111.9438	3.859344	112.682	2.683449	113.2988	2.26296	112.9114	3.469509	112.6184	3.147219	114.1152	3.371658	113.1052	3.24407

Effect of MD-960 (5mg/kg; s.c. or *i.p.*) and/or insulin (2-4U; s.c.) on body weight (g) of streptozotocin- diabetic rats

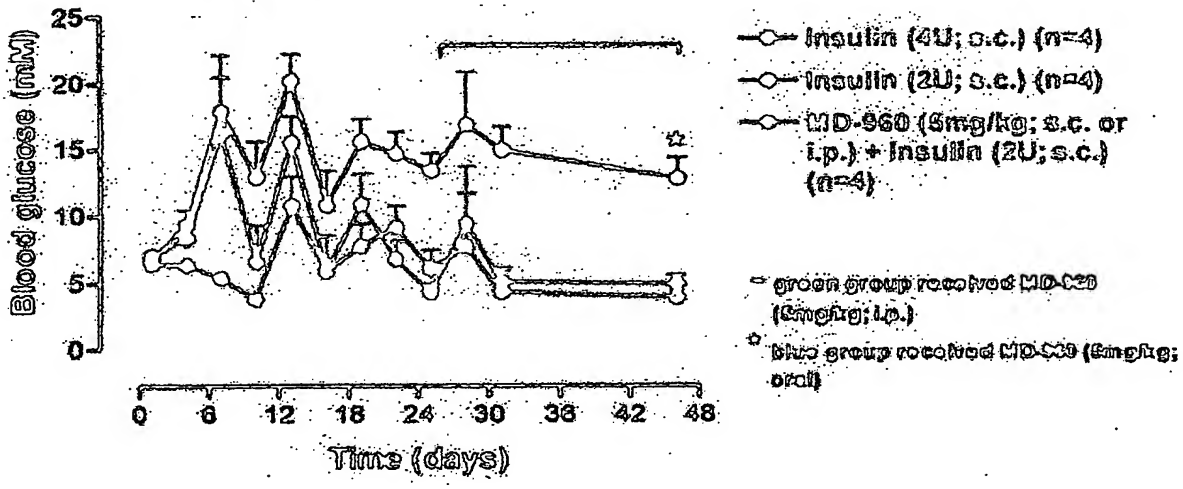


Effect of MD-960 (5mg/kg; s.c., *i.p.* or oral) and/or insulin (2-4U; s.c.) on body weight (% of original) of streptozotocin-diabetic rats

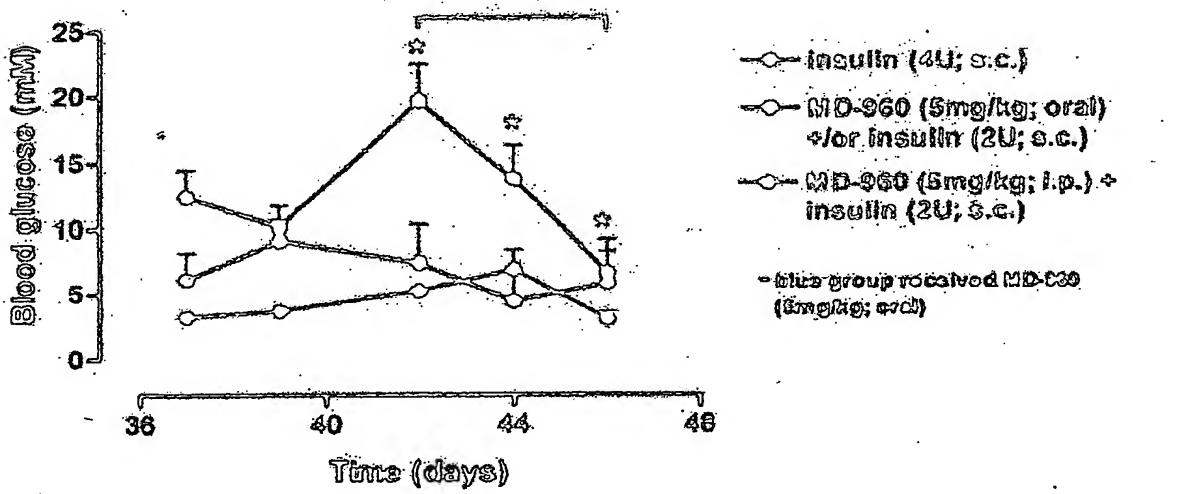


*Note: MD-960 represents Gibberellin A_3

Effect of MD-960 (5mg/kg; s.c. or *i.p.*) and/or insulin (2-4U; s.c.) on blood glucose (mM) of streptozotocin- diabetic rats 2 hours after administration



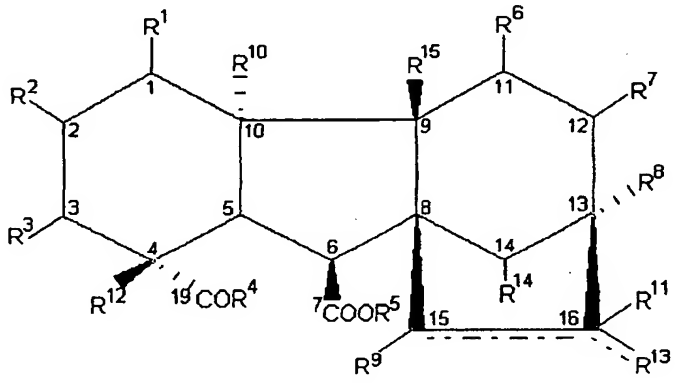
Effect of MD-960 (5mg/kg; s.c., *i.p.* or oral) and/or insulin (2-4U; s.c.) on blood glucose (mM) of streptozotocin- diabetic rats 5 hours after administration



*Note: MD-960 represents Gibberellin A_3

What is claimed is:

1. A method of treatment comprising adhibiting compounds of formula (1) (Gibberellins) and their pharmaceutically acceptable derivatives for diabetes and related conditions.



Formula (1)

wherein

R^1 is H or a group –O-R^{20}, where R^{20} is H, or together with R^2 or R^{10} forms a bond (C_1– C_2 or C_1-C_{10} double bond, respectively);

R^2 is H or a group –O-R^{21}, where R^{21} is H, a glycosylic ether group (glycoside ether) or together with R^4 forms a bond (lactone) or together with R^1 or R^3 forms a bond (C_1-C_2 or C_2-C_3 double bond, respectively);

R^3 is H, =O, or –O-R^{22}, where R^{22} is H or a glycosylic ether group (glycoside ether), or together with R^2 forms a bond (C_2-C_3 double bond);

R^4 is OH, or –OR^{23}, where R^{23} is unsubstituted or substituted $C_{1\sim20}$ alkyl, allyl, aryl, arylalkyl, amidine, -$NR^{24}R^{25}$ or an unsaturated or saturated ring containing one or more hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur; R^{24} and R^{25} may or may not be the same, are hydrogen, or $C_{1\sim20}$ alkyl, allyl, aryl, arylalkyl or an unsaturated or saturated ring containing one or more hetero-atoms slected from the group consisting of nitrogen, oxygen and sulphur; R^4 together with R^{21} or R^{28} forms a bond (lactone);

R^5 is H or a glycosylic ester (glycoside ester) group, or unsubstituted or substituted (e.g. haloginated) $C_{1\sim20}$ alkyl esters, allyl esters, aryl esters, arylalkyl esters, active esters (such as phenacyl ester, pivaloyl ester);

R^6 is H or OH or together with R^7 forms a bond (C_{11}-C_{12} double bond);

R^7 is H, =O, or $-OR^{26}$, where R^{26} is H or a glycosylic ether group (glycoside ether) or together with R^6 forms a bond (C_{11}-C_{12} double bond);

R^8 is H, hydroxyl, mercaptan, or halogen (e.g. F, Cl), amino, azido, $NR^{24}R^{25}$, unsubstituted or substituted (e.g. halogenated) $C_{1\sim20}$ alkyl, allyl, aryl, or arylalkyl, or $-OR^{27}$, where R^{27} is a glycosylic ether group (glycoside ether);

R^9 is H or OH, or together with R^{15} forms a bond (C_9-C_{15} bond);

R^{10} is H, CH_3, CHO, COOH, or a glycosylic ester (glycoside ester) of said COOH, CH_2O-R^{28} or $-OR^{28}$, where R^{28} is H or together with R^4 forms a bond (lactone) or together with R^1 forms a bond (C_1-C_{10} double bond);

R^{11} is OH or absent;

R^{12} is CH_3, CH_2OH, COOH or a glycosylic ester (glycoside ester) of said COOH;

R^{13} is methylene, or a divalent hetero-atom, or NR^{29}, where R^{29} is NR^{30} or OR^{30} where R^{30} is H, or $C_{1\sim20}$ alkyl, aryl, alkylaryl; when R^{11} is absent, a double bond is present between C_{16} and R^{13};

R^{14} is H or OH;

R^{15} is H, or together with R^9 forms a bond (C_9-C_{15} bond);

And pharmaceutically acceptable derivatives, lactones, esters and salts including alkali metal salts (e.g. Na^+, K^+), alkaline earth metal salts (e.g. Ca^{2+}, Mg^{2+}), metal salts (e.g. Zn^{2+}, Al^{3+}), and salts of ammonium, organic bases (such as $NR^{16}R^{17}R^{18}R^{19}$ where R^{16}, R^{17}, R^{18}, R^{19}, which may be the same or not the same, are hydrogen, $C_{1\sim20}$ alkyl, alkanol, arryl) thereof.

2. The method of claim 1, wherein the Gibberellins are Gibberellin A_3.

3. The method of claim 1, wherein the Gibberellins are a mixture of Gibberellin A_3 and Gibberellin A_4 and/or Gibberellin A_7.

4. The method of claim 1, wherein the pharmaceutically acceptable derivatives are salts including alkali metal salts, alkaline earth metal salts, metal salts and salts of ammonium, organic bases.

5. The method of claim 4, wherein the organic bases are $NR^{16}\ R^{17}\ R^{18}\ R^{19}$, where R^{16}, R^{17}, R^{18}, R^{19}, which may be the same or not the same, are hydrogen, substituted or unsubstituted $C_{1\sim20}$ alkyl, alkanol, aryl.

6. The method of claim 1, wherein the pharmaceutically acceptable derivatives are lactones, glycoside, esters and active esters.

7. A method of treatment of diabetes and related conditions comprising administering an effective amount of a compound of formula (1) (Gibberellins) and their pharmaceutically acceptable derivatives.

8. A method according to claim 7, wherein the Gibberellins are Gibberellin A_3.

9. A method according to claim 7, wherein the Gibberellins are a mixture of Gibberellin A_3 and Gibberellin A_4 and/or Gibberellin A_7.

10. A pharmaceutical composition comprising a compound of formula (1), as an active ingredient for the treatment of diabetes and related conditions.

11. A slow releasing or long acting pharmaceutical composition comprising a compound of formula (1) as an active ingredient for the treatment of diabetes and related conditions.

12. According to claim 11, wherein the formulation is for oral administration.

13. According to claim 11, wherein the formulation is for inhalation administration.

14. According to claim 11, wherein the formulation is for transdermal administration.

15. According to claim 11, wherein the formulation is for injection.

16. The method of treatment of diabetes and related conditions comprising compounds of formula (1) (Gibberellins) and their pharmaceutically acceptable derivatives in combination therapy with insulin and/or its fragment derivatives, and/or IGF, and/or growth factors, and/or other pharmaceutically compatible anti-diabetic agents.

17. The method according to claim 1, for the treatment of type 1 diabetes.

18. The method according to claim 1, for the treatment of type 2 diabetes.

19. The method according to claim 1, for the treatment of insulin resistant diabetes.

20. The method according to claim 1, for the treatment of diabetic related conditions including obesity, heart and eye diseases, and diabetic ulcers.

Inventors: Peter James Jenkins
Minne Wu
David Shine Wu
Australian Biomedical Company Pty. Ltd.
12th July, 2002

7 pages of animal Experiment data is attached.